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2,5-Disubstituted Pyrrolidines as Chiral Auxiliaries in Radical Reactions: A Theoretical Approach

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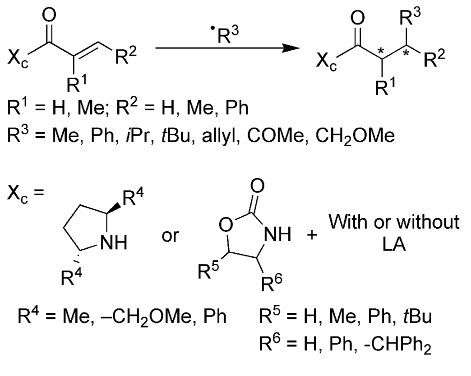
The radical addition to amides derived from chiral 2,5-disubstituted pyrrolidines has been theoretically studied by the use of density functional methods and the results compared with known experimental data. The results agree quite well with those obtained experimentally and allow the full rationalization of the factors influencing the diastereoselectivity. Steric effects are the main factors determining the selectivity, but electronic interactions can also be very important when the attacking alkene is α,β-conjugated, as in acrylic esters or acrylamides. Additions at the α- and β-positions of the amide chain in the auxiliary are subject to different rules, with the former usually yielding high diastereoselectivities both experimentally and theoretically, whereas the latter is theoretically predicted to occur with low selectivity. We fully rationalize these two opposite behaviours and suggest several ways to circumvent this limitation, thus strongly increasing the interest of this type of structure as chiral auxiliaries in radical reactions.

Introduction

Chiral auxiliaries are well-known units used in the induction of chirality in ionic reactions.[1] Several synthetic and mechanistic studies have been reported,[2,3] and steric and electrostatic effects are accepted to be the major influences determining the observed selectivities.[4–6] Usually the chiral auxiliary is connected to the substrate through an amide bond, which has a large impact on the selectivity of these systems.[4,6] Recently, chiral auxiliaries have also started to be used in the formation of carbon–carbon bonds under radical conditions, which has considerably increased their importance in organic chemistry.[7–9]

The formation of carbon–carbon bonds by free-radical addition to alkenes is of particular importance in organic synthesis. The use of this methodology has been greatly expanded by the development of new radical-chain sequences involving the formation of C–C bonds that leads to many different types of organic compounds.[10] In spite of this, organic free radicals have historically been regarded as intermediates poorly suited for selective processes due to their high reactivity. Nowadays it is accepted that steric and polar effects (and to a lesser extent, radical stabilization) play important roles in addition reactions, and the chemo- and regioselectivities of radical additions are usually predicted and rationalized on the basis of these effects.[11] Diastereoselective radical cyclization reactions have also been known for many years,[9,12] but the development of highly stereoselective intermolecular reactions involving acyclic radicals is relatively new as the control of stereoselectivity in this type of system is more difficult.[9,13]

Good performances in the use of chiral auxiliaries in intermolecular free-radical reactions motivated their extended employment in the last decade.[8,9,14,15] In almost all known studies, chiral auxiliaries similar to those employed in ionic reactions were used with the necessary modifications in the substrate to allow their application in radical processes (Scheme 1).[16,17] The best selectivities were obtained by using chiral auxiliaries that allow for the formation of chelated complexes with selected Lewis acids[16–18] according to methodologies similar to those already used in



Scheme 1. Examples of asymmetric radical addition reactions of chiral pyrrolidine and oxazolidinone derivatives with or without Lewis acid catalysis.

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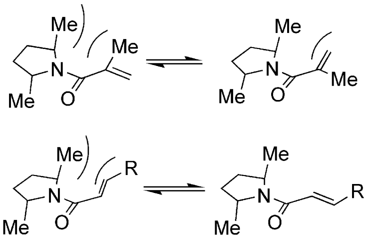
ionic reactions. In spite of this effort, stereochemical control in radical reactions is still not well understood, and the mechanisms proposed are mainly empirical and based on their ionic counterparts.[9,19,20]

In this manuscript we present a theoretical study of the radical addition of different olefins to amide derivatives of the chiral auxiliary *trans*-2,5-dimethylpyrrolidine (Scheme 2). The two C_2-symmetric configurations of this compound have previously been used as chiral auxiliaries in several radical reactions, inducing good to very good selectivities.[9,21,22] As they are very simple C_2-symmetric molecules that do not allow for electrostatic contacts or for the formation of chelated structures, when connected to the substrate through an amide bond they create two diastereofaces that differ only in the different distances between the reactive carbon centre and the pyrrolidine methyl substituents (Scheme 2).



Scheme 2. *trans*-2,5-Dimethylpyrrolidine as chiral auxiliary. The most important steric contacts and the induction of two diastereofaces due to the C_2 symmetry of the pyrrolidine ring are shown.

Our study was first aimed at the validation of our theoretical model by the rationalization of the selectivities observed by Porter et al.[21] in the radical addition of different olefins to amide derivatives of (2*R*,5*R*)-2,5-dimethylpyrrolidine (Scheme 3). The study was then extended to other systems with modifications at the olefin or the auxiliary moieties and with or without the inclusion of Lewis acids as catalysts. The results obtained should allow an understanding of the importance of the relative group bulkiness, the minimal distances between bulky groups and the relative importance of electronic and steric effects in the induction of high reaction selectivities. At the same time, this study may be of major importance for the rationalization of selectivities observed in radical reactions with more complex chiral auxiliary derivatives, in particular, those that allow for strong electrostatic effects and also those in which chelating processes can have a major role.[16–18]

Results and Discussion

The C_2-symmetric isomers of 2,5-dimethylpyrrolidine are structures that can induce diastereoselectivity, apparently due to differentiated steric interactions between their methyl substituents and the various attacking species, either in ionic or radical processes. This means that if the reacting centre is near the amine moiety, stronger contacts can arise, and higher selectivity should be obtained. On the other hand, a reactive centre directly bound to the nitrogen atom would induce no selectivity as it is located at the C_2 symmetry axis (Figure 1).

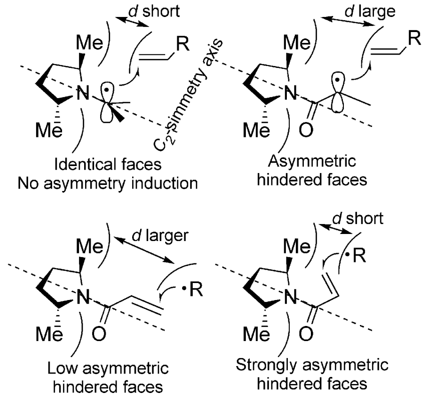
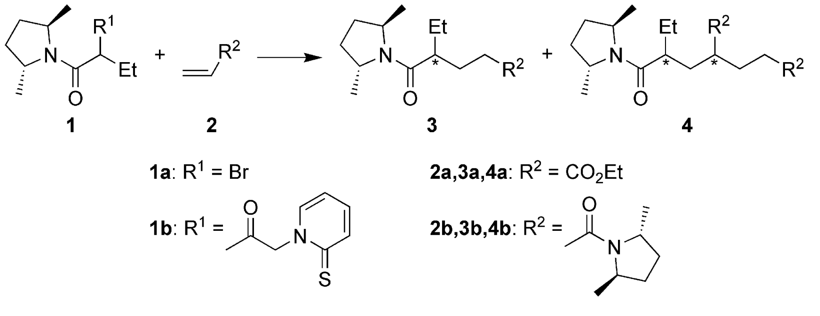


Figure 1. Relationship between the pyrrolidine asymmetry induction, the distance to the symmetry axis of the reactive centre and the distance from the reactive centre to the pyrrolidine substituents.

The existence of an amide bond, due to its 120° valence angle, leads to different distances (*d*, in Figure 1) between the α-carbon atom and each of the methyl groups, thus inducing two diastereofaces at this position. The drawback is that the existence of two bonds between the reactive centre and the amine moiety effectively increases the distance to the bulky methyl groups, thus reducing their steric contact with the attacking species (Figure 1).

If the reactive centre is the β-atom, as is the case in α,β-conjugated systems, and the molecule adopts the s-*cis* conformation, the distance to the bulky methyl groups in-



Scheme 3. Reaction selectivities observed by Porter et al.[21] in the addition of radicals formed from structure **1** to different olefins.

creases, but the distance to the C_2 symmetry axis is maintained. Thus, a strong reduction of the steric contacts between the attacking molecule and the methyl groups in the auxiliary ring is expected with a consequent reduction in reaction selectivity. On the other hand, if the molecule adopts the s-*trans* conformation, the distance between the β-atom and one of the methyl groups decreases, and the distance to the C_2 symmetry axis increases (Figure 1) or, in other words, better stereodifferentiation can be expected between the two diastereofaces.

The statements above indicate that although the distance between the amide methyl groups and the attacking species has to be as short as possible, the position of the reactive centre relative to the C_2 symmetry axis may be of major importance as this defines the extension of the asymmetry between the two diastereofaces. We will first analyse these two effects by changing the position of the reactive centre (α or β, relative to the carbonyl group and s-*cis*/s-*trans* conformation), as well as the bulkiness of the amine substituents or the attacking species, and then the improvement in selectivity that can result from the use of achiral Lewis acids as catalysts bound to the amide oxygen atom.

The reaction reported by Porter et al.[21] is based on (2*R*,5*R*)-2,5-dimethylpyrrolidine as a chiral auxiliary and involves a two-step mechanism: a radical (**5**) is generated at the α-carbon atom (Scheme 4) by a conventional tin hydride methodology and is followed by the attack of an olefin (acrylic ester or acrylamide). The radical is supposed to be planar, and thus the transition state of the addition step controls the final stereochemistry. The final products **3a** and **3b** are mixtures of two stereoisomers, (*S*) and (*R*) (**3a**: 92.3:7.7; **3b**: 96.2:3.8; reaction at 80 °C) with some by-products **4a** or **4b** (Scheme 3), which result from the addition of a second molecule of acrylate or acrylamide, respectively.

Before any attempt to study the transition states (TSs) of the addition step, it is necessary to study the geometry of radical **5**. As seen in Figure 2, the carbon radical adopts a conformation that is coplanar with the auxiliary ring and the carboxy group due to conjugation with the amide moiety. The radical chain can adopt two different conformations, (*Z*) and (*E*), the former being about 21 kJ mol⁻¹ more stable than the latter. Thus, we can neglect the participation of the (*E*) conformation in the reaction pathway. The (*Z*) conformer can also adopt two possible conformations around the C_α–C_β bond (Figure 2) that are energetically very similar (0.4 kJ mol^{-1}). As the two conformations coexist in a fast equilibrium, the most stable will be used as the energy reference.

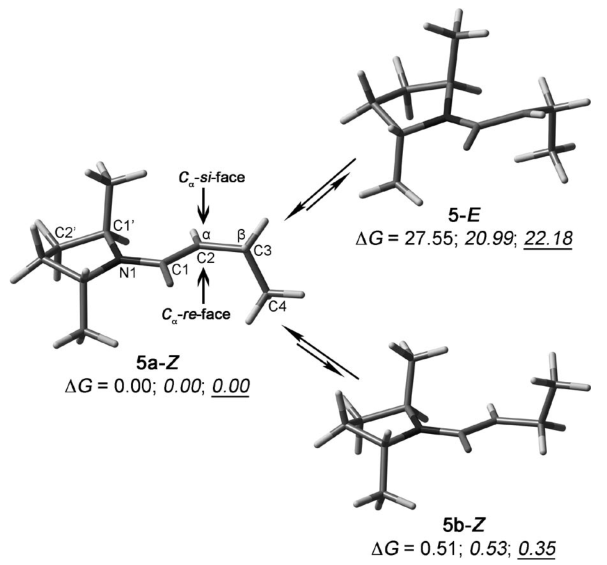
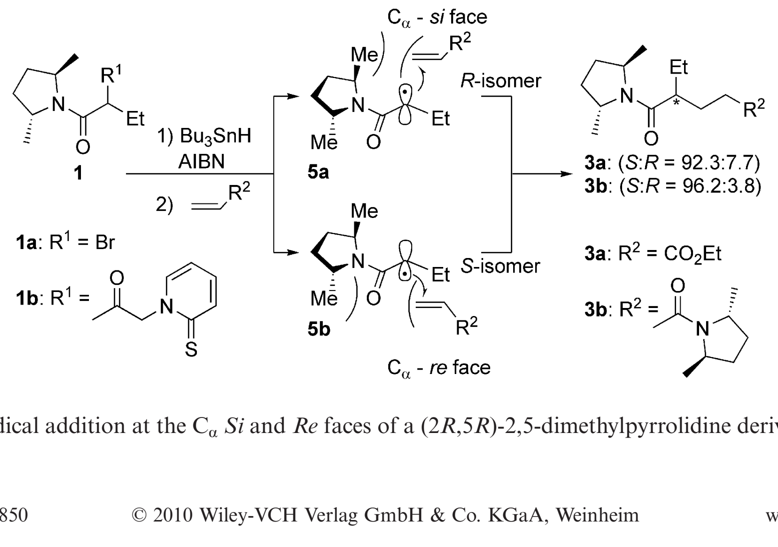


Figure 2. Three possible conformations of radical **5**. The relative energies were calculated in the gas phase (normal) and with the polarizable continuum model [PCM; *italic* (CH_2Cl_2), *italic* and underlined (C_6H_6, 80 °C)] at the UMP2/6-31G**//UBHandHLYP/6-31G** level. Energies in kJ mol^{-1}.

An acrylate molecule can approach radical **5** at the C_α *Re* or *Si* faces through several possible conformations, which originate an identical number of possible transition states. The selectivities presented in Table 1 were calculated by using three conformations for the attack at the C_α *Si* face and eight conformations for the attack at the C_α *Re* face, but Figure 3 only shows the two most stable TSs for the attack at each face. As the s-*cis*/s-*trans* equilibrium of the attacking acrylate is only slightly shifted to the s-*cis* side (Δ*G* ≈ 3.1 kJ mol^{-1}), both conformations were considered in the transition states.



Scheme 4. Stereoselective radical addition at the C_α *Si* and *Re* faces of a (2*R*,5*R*)-2,5-dimethylpyrrolidine derivative, as proposed by Porter et al.[21]

Table 1. Experimentally[21] determined and theoretically predicted diastereomeric ratios, calculated in the gas phase and with the PCM (CH_2Cl_2 or C_6H_6) at the UMP2/6-31G**//UBHandHLYP/6-31G** level for the reaction between radical **5** and acrylic ester **2a** or acrylamide **2b**.

Entry	*T* [°C]	Acrylate	Ratio (*S*)/(*R*)		
			Gas phase	Solvent	Ref.[21]
1	80	**2a**	95.7:4.3	97.6:2.4[a]	92.3:7.7[a]
2		**2b**	94.8:5.2	98.7:1.3[a]	96.2:3.8[a]
3	25	**2a**	97.0:3.0	98.9:1.1[b]	96.2:3.8[b]
4		**2b**	95.6:4.4	99.7:0.3[b]	–
5	–24	**2a**	98.2:1.8	99.5: 0.5[b]	97.3:2.7[b]

[a] In benzene. [b] In dichloromethane.

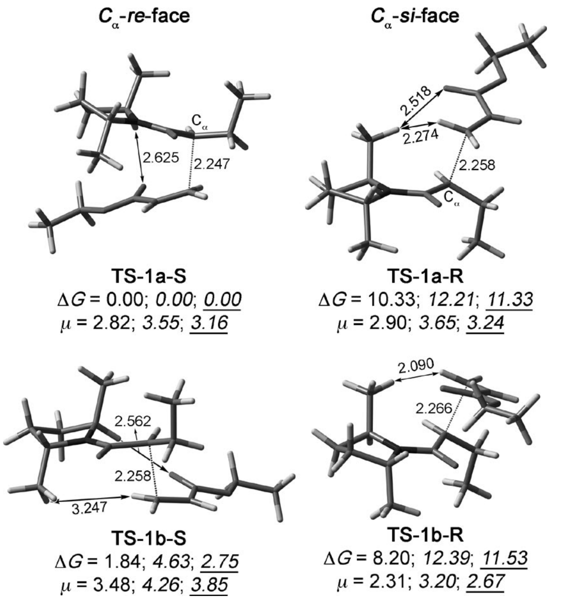


Figure 3. Most stable transition-state structures for the addition of ethyl acrylate (**2a**) to radical **5** at both diastereofaces. The relative energies were calculated in the gas phase (normal) and with the PCM [*italic* (CH_2Cl_2), *italic* and underlined (C_6H_6, 80 °C)] at the UMP2/6-31G**//UBHandHLYP/6-31G** level. Energies in kJ mol^{-1} and distances in Å.

The theoretical values agree quite well with the experimental results, predicting a preferential attack at the C_α *Re* face with the consequent formation of the (*S*) isomer in a ratio of 97.6:2.4 at 80 °C in benzene (experiment: 92.3:7.7 in benzene at 80 °C). The theoretical temperature dependence is also in agreement with the experiment, with better selectivity predicted at lower temperatures (Table 1, Entries 3 and 5). The experimental improvement in the selectivity in solvent also fits our theoretical data and, according to our calculations, is a result of the relative dipolar moments of the two diastereomeric TSs as (*S*) transition states (attack at the C_α *Re* face) are more polar and thus more stabilized in solvent.

In ionic additions to groups bound to chiral auxiliaries, the selectivity is usually a result of steric and/or electrostatic interactions between the attacking group and the substituents on the chiral auxiliary moiety.[3,5] If a similar explanation is used to justify the selectivity observed in the system studied here, then it would be expected that the attacking ester has to be orientated in a way that reduces the steric contacts with the methyl groups in the pyrrolidine moiety. Nevertheless, and as seen in Figure 3, the lowest energy conformer for the attack at the C_α *Re* face adopts a relative orientation of the two reacting species that forces the bulkiest groups in the alkene to have strong steric contacts with the methyl groups in the auxiliary ring. This result is unexpected if only steric and electrostatic contacts are taken in account, but can be explained if electronic effects are also considered. Figure 4 displays the SOMO orbitals for the attack at both diastereofaces (lowest-energy conformers) and indicates that the reaction at the C_α *Re* face allows for a secondary orbital interaction (SOI) between the π-system of the attacking molecule and the nitrogen atom in the auxiliary ring that reduces the activation energy of the TS. When the attack occurs at the C_α *Si* face, a similar approach of the two reacting molecules is not possible as a strong steric contact with one of the methyl groups in the auxiliary would result. To minimize this contact, the two molecules have to rotate approximately 180°, thus eliminating the SOI observed in the attack at the C_α *Re* face, with a consequent energy increase. The importance of the SOI becomes evident if we compare the energy of the second-lowest energy TSs for the attack at both faces. In this case, in both structures the ester moiety is away from the hindered chiral auxiliary moiety but, whereas the two C_α *Si*-face TSs have nearly the same activation energy, there is a difference of around 4.5 kJ mol^{-1} between the two C_α *Re*-face TSs (see Figure 3; CH_2Cl_2).

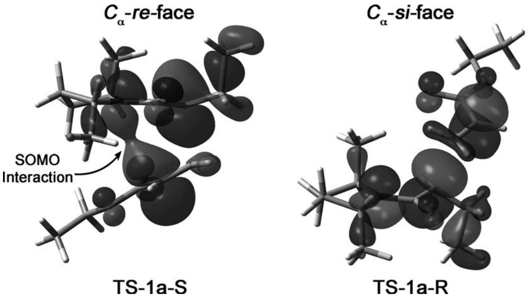


Figure 4. SOMO orbitals of the most stable transition-state structures obtained in the addition of ethyl acrylate (**2a**) to radical **5** at both diastereofaces. Isosurfaces at 0.03 a.u. were calculated with the PCM at the UMP2/6-31G**//UBHandHLYP/6-31G** level.

On the basis of the above discussion, the introduction of larger groups into the alcohol moiety of the acrylate molecule is expected to reduce the reaction selectivity because, in the lowest-energy conformer for the attack at the C_α *Re* face, this should increase the steric contacts with the methyl groups in the auxiliary ring, thus increasing its energy. A smaller effect is expected for the attack at the C_α *Si*-face TSs as a result of their preferred conformations, thus resulting in an overall reduction of selectivity.

In contrast to the idea discussed above, the results reported by Porter et al.[21] for the addition of amide **2b** to radical **5** suggest that the use of larger groups in the acrylate substantially improves the reaction selectivity. To gain an understanding of this apparent contradiction, we also studied the addition of amide **2b** to radical **5**, and the results are reported in Table 1 and Figure 5. As the s-*cis*/s-*trans* equilibrium of the acrylamide is strongly shifted to the s-*cis* side ($\Delta G \approx 10\,\mathrm{kJ\,mol^{-1}}$), only this conformation was considered in the TSs.

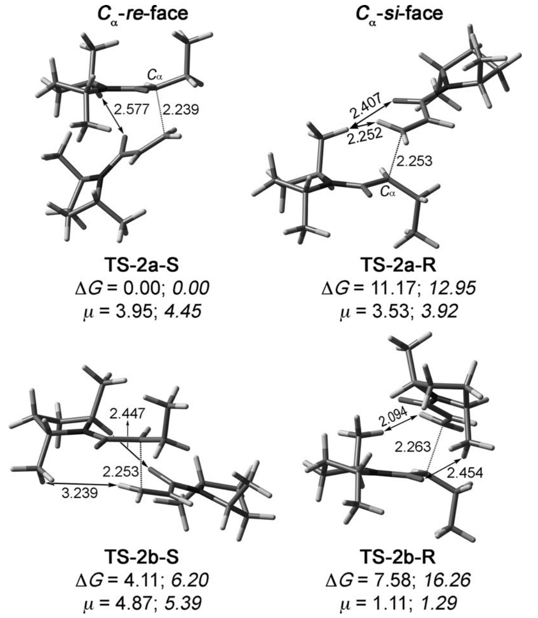
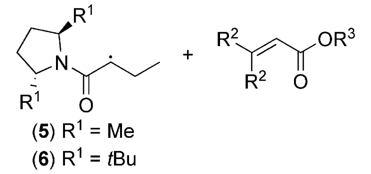


Figure 5. Most stable transition-state structures for the addition of acrylamide **2b** to radical **5** at both diastereofaces. The relative energies were calculated in the gas phase (normal) and with the PCM [*italic* (C_6H_6, 80 °C)] at the UMP2/6-31G**//UBHandHLYP/6-31G** level. Energies in $\mathrm{kJ\,mol^{-1}}$ and distances in Å.

The values in Table 1 (Entries 2 and 4) are quite interesting as they indeed predict a reduction of selectivity in comparison with Entries 1 and 3, respectively, if the calculation is made in the gas phase. This is a result of stronger steric contacts in the (*S*) transition states as a result of the increased bulkiness of the amide of dimethylpyrrolidine (compare Figures 3 and 5), as was previously discussed. Nevertheless, if solvent effects are considered, the predicted selectivity values increased considerably (Table 1, Entries 2 and 4; solvent) and are larger than the values obtained with **2a** (Entries 1 and 3), in agreement with experiment. These results indicate that the higher selectivity obtained with amide **2b** is not a result of its larger size in comparison with the ester, but a result of electrostatic effects, either dipole moments or intermolecular electrostatic contacts. In general, the dipole moments of the (*S*) transition-state structures (attack at the C_α *Re* face) are larger and thus more stabilized in solvent (see Figures 3 and 5). The result is a selectivity increase in both systems when solvent is included in the calculations, but with a larger effect in the amide addition as the difference in the dipole moments between the two diastereofacial TSs is also larger.

The results discussed above confirm our initial prediction, that larger ester or amide groups in the attacking molecule should reduce the final selectivity, unless these groups induce dipolar moments in the TS structures that can compensate the steric effects, as is the case when the ester is replaced by an amide group. This means that any attempt to improve the selectivity by improving the selective steric repulsion between the two reacting species has to be realized at the acrylate β-carbon atom or at the methyl substituents in the pyrrolidine ring. With this in mind, we studied the addition of several acrylate derivatives to radical **5** and to other similar radicals based on auxiliary derivatives with bulkier substituents. The results are summarized in Table 2, and selected structures are presented in Figure 6.

Table 2. Theoretically predicted diastereomeric ratios in the gas phase and in dichloromethane calculated at the UMP2/6-31G**//UBHandHLYP/6-31G** level for the reaction of radical **5** or **6** with several acrylates at 25 °C.



Entry	Radical	R^2	R^3	Ratio (*S*)/(*R*) Gas phase	Ratio (*S*)/(*R*) CH_2Cl_2
1	**5**	H	Et	97.0:3.0	98.9:1.1
2	**5**	H	Me	96.6:3.4	98.7:1.3
3	**5**	F	Me	96.8:3.2	98.3:1.7
4	**5**	Me	Me	99.5:0.5	99.6:0.4
5	**5**	*t*Bu	Me	99.98:0.02	100.0:0.0
6	**6**	H	Me	99.99:0.01	99.98:0.02

Entry 3 in Table 2 indicates that small electronegative groups at the acrylic β-position are not expected to affect the selectivity because the TSs can adopt several conformations around the forming bond that allow for efficient reduction of the electrostatic repulsion without strongly increasing the steric repulsions or affecting the electronic interactions observed in the attack at the C_α *Re* face.

The data in Table 2 show that the introduction of two methyl groups at the β-carbon atom (Entry 4) of the acrylate moiety substantially improves the selectivity as the energy difference between the two most stable conformers for the attacks at each diastereoface increases from $11.3\,\mathrm{kJ\,mol^{-1}}$ (**TS-1a-R**, Figure 3) to $14.1\,\mathrm{kJ\,mol^{-1}}$ (**TS-4a-R**, Figure 6). The use of *tert*-butyl groups leads to an increase in this difference to $21.4\,\mathrm{kJ\,mol^{-1}}$ (**TS-5a-R**, Figure 6) with the corresponding increment in selectivity (Table 2, Entry 5). Entry 6 in Table 2 indicates that larger groups (*t*Bu) in the auxiliary are more efficient in improving the selectivity, the calculations predicting maximum selectivity even when there are no substituents at the acrylate β-carbon atom. This happens because when the *tert*-butyl groups are located in the attacking acrylate, the TSs adopt conformations that increase the distance between the *tert*-butyl groups and the auxiliary substituents (Figure 6), thus reducing the steric contacts and preventing maximized selectivity. This adjustment cannot happen when the *tert*-butyl groups are in the auxiliary ring, and the net result is an improvement in the predicted diastereoselectivity. In this case, the steric repulsion in the attack at the C_α *Si* face is

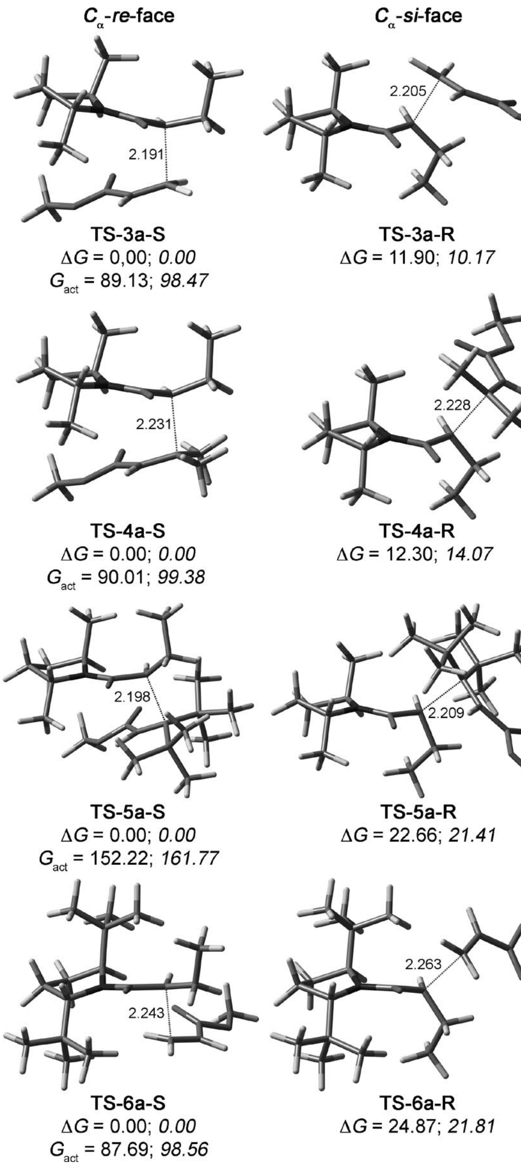
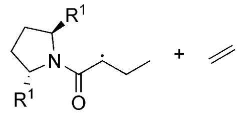


Figure 6. Most stable transition-state structures for the addition of acrylates to radicals **5** and **6** at both diastereofaces. The relative energies were calculated in the gas phase (normal) and with the PCM (*italic*) at the UMP2/6-31G**//UBHandHLYP/6-31G** level. Energies in kJ mol^{-1} and distances in Å.

so large that it even compensates for the loss of the SOI observed in the attack at the C_α *Re* face (Figure 6). The use of larger substituents in the pyrrolidine ring has a second important advantage: if *tert*-butyl groups are used instead of methyl groups as the ring substituents, the activation energy increases by only around 20 kJ mol^{-1}, whereas the use of this group as a substituent at the acrylic β-position increases the activation energy by around 83 kJ mol^{-1} due to very large steric contacts with the radical chain.

From the statements above, we are tempted to suggest that the selectivity of α-radical additions may always originate very high selectivities if the substituents in the pyrrolidine ring are larger than simple methyl groups. Nevertheless, on the basis of the geometries of the TS structures, the atoms directly bound to the pyrrolidine ring have to be tetrasubstituted. For instance, ethyl or isopropyl groups are not predicted to induce high selectivity as they behave as methyl groups with one hydrogen atom orientated towards the attacking acrylate, thus inducing weak steric interactions (Table 3). Even 2,5-diphenylpyrrolidine,[23] which has been used as a chiral auxiliary in several ionic[24,25] and radical reactions,[26] is predicted to induce selectivities (Entry 5) lower than those calculated for the smaller methyl group (Entry 1). This happens because the phenyl ring adopts an orientation that is perpendicular to the radical chain, thus reducing the steric contacts with the attacking alkene.

Table 3. Theoretically predicted diastereomeric ratios in the gas phase and in dichloromethane calculated at the UMP2/6-31G**//UBHandHLYP/6-31G** level for the reaction between radicals **5**–**9** and ethylene at 25 °C.[a]



Entry	Structure	Ratio (*S*)/(*R*)	
		Gas phase	CH_2Cl_2
1	**5**: R^1 = Me	95.2:4.8	96.0:4.0
2	**6**: R^1 = *t*Bu	99.8:0.2	99.96:0.04
3	**7**: R^1 = Et	96.7:3.3	97.5:2.5
4	**8**: R^1 = *i*Pr	94.8:5.2	96.4:3.6
5	**9**: R^1 = Ph	80.9:19.1	78.0:22.0

[a] Note: The selectivities were calculated in the transition-state structures, with the olefin accounting for group priority 2, as the products have no chiral centre at the α-position.

If the selectivity of radical addition at the α-position is highly dependent on the chiral auxiliary substituents and also on the bulkiness of the attacking molecule, this dependence should be even more important if the attack occurs at the β-position of an s-*cis* α,β-conjugated system (Figures 1 and 7), because the distance to the auxiliary increases, whereas the distance to the symmetry axis does not change, as discussed above (Figure 1). Entries 1 and 2 in Table 4 show the predicted selectivities calculated for the addition of methyl and *tert*-butyl radicals, respectively, to the crotonyl amide **10** (R^1 = Me) in the more stable s-*cis* conformation. The results are interesting, because they indeed predict low selectivity, but with opposite signs. While the methyl radical attacks at the less hindered face, the *tert*-butyl radical does the opposite. This is a clear indication that there is no interaction between the attacking radicals and the methyl groups in the auxiliary, as this type of steric effect would induce the same final configuration for the attack of both species, but with an expected higher ratio for the bulkier radical (see distances between the attacking radicals and the methyl substituents in the pyrrolidine moiety in Figure 7). Instead of resulting from steric contacts between the attacking radicals and the pyrrolidine substituents, the selectivities calculated for these two reactions result from different relaxations of the carbon chain in the transition states of the radical addition reactions. As the methyl group is small and does not strongly interact with the surrounding atoms, the carbon chain can freely adapt to the TS configuration. In contrast, the *tert*-butyl group does not allow for the best conformation of the carbon chain in the radical TSs and induces a different and opposite selectivity. This effect can be observed in the angles shown in Figure 7. Although in the initial alkene this angle is 11.4°, in **TS-7a-S** it changes to 17.9° and to 1.4° in **TS-7a-R**, which indicates that both structures can relax substantially. The angular modification is more favourable in **TS-7a-S** as it increases the distance between the α-hydrogen atom in the carbon chain and one of the methyl groups in the auxiliary, as shown in Figure 7. On the other hand, in **TS-8a-S** the value is very similar (10.2°) to that of the reagent, which indicates that no chain relaxation is possible, whereas it changes to 5.0° in **TS-8a-R**, which indicates some relaxation. Thus, whereas **TS-7a-S** is more stable than **TS-7a-R**, the opposite is true for the attack of the *tert*-butyl radical. Entries 3 and 4 in Table 4 show the selectivities predicted when the methyl groups in the pyrrolidine ring are replaced by *tert*-butyl groups. Steric contacts between the attacking radicals and the pyrrolidine substituents are observed in these additions, but the effect discussed above still renders the calculated selectivity of the methyl radical attack higher than that of the *tert*-butyl radical attack, and still of opposite sign.

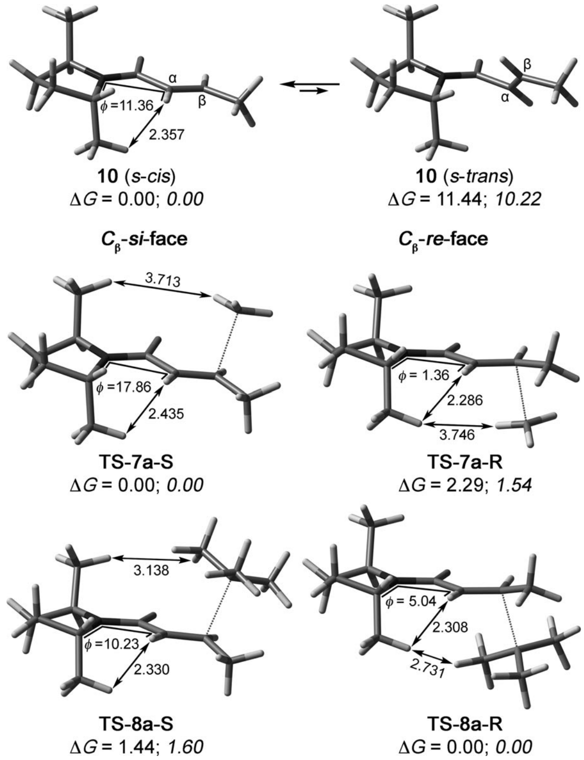
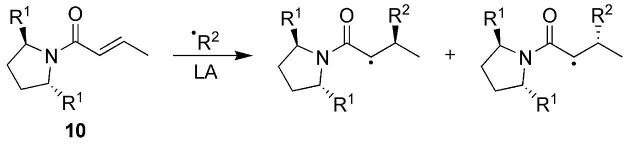


Figure 7. Two possible conformations of the C_α–C_β bond in amide **10** and the TS structures for the addition of methyl or *tert*-butyl radicals. The relative energies were calculated in the gas phase (normal) and with the PCM (*italic*) at the UMP2/6-31G**//UBHandHLYP/6-31G** level. Energies in kJ mol^{-1} and distances in Å. To simplify the discussion, in the assignment of the absolute configuration of **TS-7a**, the attacking radical was given the group priority 1.

Table 4. Theoretically predicted diastereomeric ratios in the gas phase and in dichloromethane calculated at the UMP2/6-31G**//UBHandHLYP/6-31G** level for the reaction between **10** and several radicals with and without a Lewis acid at 25 °C.



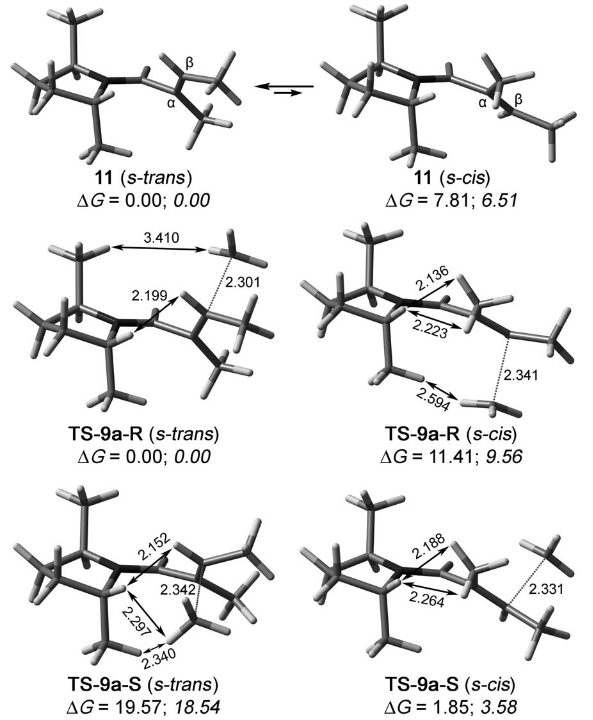
Entry	Lewis acid	Structure	Ratio (*S*)/(*R*) Gas phase	Ratio (*S*)/(*R*) CH_2Cl_2
1	–	R^1 = Me, R^2 = Me[a]	71.6:28.4	65.0:35.0
2	–	R^1 = Me, R^2 = *t*Bu	35.8:64.2	34.5:65.5
3	–	R^1 = *t*Bu, R^2 = Me[a]	70.8:29.2	70.6:29.4
4	–	R^1 = *t*Bu, R^2 = *t*Bu	26.6:73.4	41.7:58.3
5	$AlCl_3$	R^1 = Me, R^2 = Me[a]	91.6:8.4	78.9:21.1
6	$AlCl_3$	R^1 = Me, R^2 = *t*Bu	92.1:7.9	85.2:14.8
7	$AlCl_3$	R^1 = *t*Bu, R^2 = Me[a]	79.9:20.1	82.6:17.4
8	$AlCl_3$	R^1 = *t*Bu, R^2 = *t*Bu	92.1:7.9	91.7:8.3

[a] The selectivities were calculated in the transition-state structures, with the attacking radical accounting for group priority 1, as the products have no chiral centre at the β-position.

From the analysis of the results in Entries 1–4 in Table 4 we can indeed conclude that if the crotonyl chain is in an s-*cis* conformation, high selectivities are not expected in radical additions to the β-carbon atom. Nevertheless, if the conformation of the crotonyl chain is s-*trans* [see Figure 7, structure **10** (*s-trans*)], higher selectivities can be expected as the β-carbon atom is much nearer to the chiral auxiliary and at the same time further away from the symmetry axis.

To form a stable s-*trans* conformer it is necessary for a substituent to be introduced at the α-carbon atom. For instance, the α-methylcrotonamide **11** mainly exists in the s-*trans* conformation (ΔG = 6.5 kJ mol^{-1}; Figure 8), whereas the unsubstituted derivative **10** exists mainly as the s-*cis* conformer (ΔG = 10.2 kJ mol^{-1}; Figure 7). The selectivity predicted for the radical addition to compound **11**, considering two diastereomeric pathways via the s-*trans* conformer, is 99.9% (*R*) if the substituents at the pyrrolidine ring are methyl groups and 100% (*R*) if they are *tert*-butyl groups. These values are slightly reduced if the s-*cis*⇌s-*trans* equilibrium is considered because the two extra reaction pathways also afford high selectivity but of opposite sign, thus reducing the overall predicted value (Figure 8 and Table 5). In the unsubstituted derivative **10** this conformational equilibrium is not relevant as the difference between the two conformers is larger (ΔG = 10.2 kJ mol^{-1}), as stated above (see also Figure 7).

The result predicted for the radical addition to compound **11** by the s-*cis* reaction pathway is quite interesting. In contrast to the value obtained for the unsubstituted derivative **10**, high selectivity is predicted, even when the attacking radical is a simple methyl group. This happens because the methyl substituent at the α-position of the crotonyl chain destroys the coplanarity of the structure and induces a higher degree of asymmetry between the two diastereofaces with one of them being substantially more hin-



11 (*s-trans*) ΔG = 0.00; *0.00* **11** (*s-cis*) ΔG = 7.81; *6.51*

TS-9a-R (*s-trans*) ΔG = 0.00; *0.00* **TS-9a-R** (*s-cis*) ΔG = 11.41; *9.56*

TS-9a-S (*s-trans*) ΔG = 19.57; *18.54* **TS-9a-S** (*s-cis*) ΔG = 1.85; *3.58*

Figure 8. Two possible conformations around the C_α–C_β bond in amide **11** and the calculated TSs for the addition of the methyl radical. The relative energies were calculated in the gas phase (normal) and with PCM (*italic*) at the UMP2/6-31G**//UBHandHLYP/6-31G** level. Energies in kJ mol^{-1} and distances in Å. To simplify the discussion, in the assignment of the absolute configuration of the TSs, the attacking radical was given the group priority 1.

dered by one of the methyl groups in the auxiliary ring (Figure 8). On the other hand, in the unsubstituted compound **10**, the structure is coplanar and both faces are very similar as the β-carbon atom is quite distant from the auxiliary substituents (compare Figures 7 and 8).

To circumvent the low selectivity obtained in radical additions at the β-position of amides **10** of pyrrolidine, about 10 years ago Sibi et al.[16] adopted a methodology already used in ionic reactions that involves the use of chiral oxazolidinone derivatives instead of amides of pyrrolidine (Scheme 1). It is supposed that such structures form chelated complexes with selected Lewis acids and that the resulting locked conformer can induce higher selectivity, either in ionic or radical processes, as was indeed observed (Figure 9).

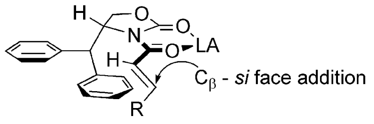


Figure 9. Asymmetric radical addition induced by a chiral auxiliary in the presence of a Lewis acid.[16]

A recent paper from Daasbjerg, Skrydstrup and coworkers[19] strongly supports this idea as they were able to show that the reactivity of SmI_2-promoted radical additions of acrylamides to *N*-acyloxazolidinones is directly correlated with the activation energies calculated for the amide bond rotation of the oxazolidinones, which indicates that chelation with the Lewis acid takes place before the radical addition step. Nevertheless, we recently proposed an alternative mechanism that does not involve chelate formation but that properly explains the selectivities observed in Lewis acid (LA) catalyzed Diels–Alder addition reactions and also allows the rationalization of other results reported in the literature (Figure 10).[4] As shown in Figure 10, the isopropyl substituent forces the LA to adopt a conformation above the molecular plane (C_β *Re* face), which hinders the attack of dienes at this face. On the other hand, the isopropyl group is not able to hinder attack at the opposite face as it is too distant from the reactive centre. The net

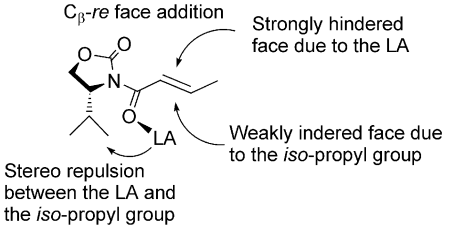
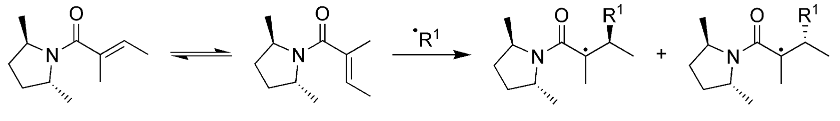


Figure 10. Asymmetric Diels–Alder reaction induced by a chiral auxiliary in the presence of a Lewis acid.[4]

Table 5. Theoretically predicted diastereomeric ratios calculated at the UMP2/6-31G**//UBHandHLYP/6-31G** level for the reaction between amide **11** and methyl or *tert*-butyl radicals in the gas-phase (normal) or in CH_2Cl_2 (*italic*).



11 - *cis* **11** - *trans*

Entry	Structure	Ratio (*R*)/(*S*)		
		s-*cis*	s-*trans*	s-*cis* + s-*trans*[b]
1	R^1 = Me[a]	2.07:97.93	99.96:0.04	97.97:2.03
		8.23:91.77	*99.94:0.06*	*98.27:1.73*
2	R^1 = *t*Bu	5.80:94.20	100.00:0.00	99.96:0.04
		23.01:76.99	*100.00:0.00*	*99.98:0.02*

[a] The selectivities were calculated in the transition-state structures, with the attacking radicals accounting for group priority 1, as the products have no chiral centre at the β-position. [b] The selectivity was calculated taking into account the s-*cis*/s-*trans* equilibrium.

result is a preferential attack on the same face as the isopropyl substituent.

If the principles discussed above are applied to radical addition reactions, an improvement in selectivity can be expected for the addition of methyl or *tert*-butyl radicals to structures of type **10** (Figure 7) if they are previously complexed to a Lewis acid. Entries 5–8 in Table 4 show the selectivities predicted for radical addition to complexes of **10** and aluminium trichloride, which, by comparison with the values calculated in the absence of LA, indicate that a large improvement in selectivity is indeed expected (Table 4). Analysis of the 3D structures in Figure 11 allows the rationalization of these results. When a LA forms a complex with the carbonyl oxygen atom, it orientates to minimize the steric interaction with the substituents in the pyrrolidine ring (complex **10**/$AlCl_3$; Figure 11). If radical attack occurs at the C_β *Si* face, the LA is away from the attacking radical and away from the pyrrolidine substituent. As the attacking radical only weakly interacts with the pyrrolidine substituents, the steric energy is low. On the other hand, if the attack occurs at the C_β *Re* face, the LA group is forced to move away from the attacking radical and has to approach the pyrrolidine substituent, thus increasing the steric energy. The net result is a predicted improvement in the reaction selectivity.

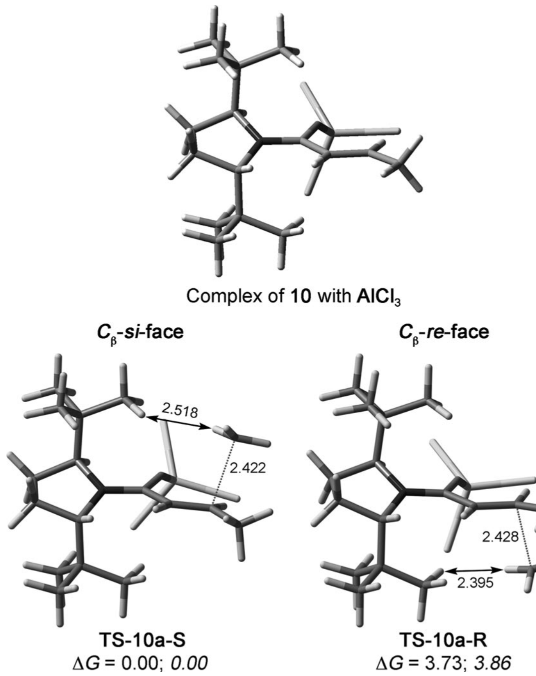


Figure 11. Most stable transition-state structures for the addition of the methyl radical to the complex **10**/$AlCl_3$ at both diastereofaces. The relative energies were calculated in the gas phase (normal) and with the PCM (*italic*) at the UMP2/6-31G**//UBHandHLYP/6-31G** level. Energies in kJ mol^{-1} and distances in Å.

The mechanism proposed above does not disclose a possible existence of chelated complexes in systems that can form them, but allows for a possible development of new systems based on simple molecules that can induce high stereoselectivities without the need of chelating conditions or chelating LAs. To the best of our knowledge, nobody has attempted such an approach with radical systems, but a paper from Hajra et al.[25] shows that this approach indeed works in ionic processes, in Lewis acid catalyzed asymmetric bromoazidation reactions of chiral α,β-unsaturated carbonyl compounds with NBS and $TMSN_3$. In this study, the use of (2*S*,5*S*)-2,5-diphenylpyrolidine as the chiral auxiliary yielded much better results than the Evans auxiliary or bornanesultam when using $Yb(OTf)_3$ as the Lewis acid.

Conclusions

In this study we have been able to show that the stereoselectivity observed in radical additions to amides derived from chiral 2,5-disubstituted pyrrolidines can be fully rationalized on the basis of steric and electronic effects. Although steric effects are always present, electronic effects were only observed when the attacking species is α,β-conjugated, as in acrylic esters or acrylamides. The geometry of the amide chain in the auxiliary is irrelevant for the selectivities obtained in additions at the α-position, but becomes of major importance when attack occurs at the β-carbon atom. Thus, our calculations suggest that good selectivities in radical additions at this atom can indeed be obtained if careful control of the chain geometry is observed. On the other hand, good improvements in selectivity are also expected if achiral Lewis acids are used as catalysts in radical additions at the β-position. Based on our data, the rationalization of experimental results obtained with more complex chiral auxiliaries is now possible, and the improvement of known chiral auxiliaries can be expected.

Computational Details

Full geometry optimizations were performed with the Gaussian 03[27] suite of programs by employing density functional theory (DFT)[28] with the unrestricted hybrid half-and-half functional (UBHandHLYP)[29,30] and the 6-31G** basis set. Harmonic vibrational frequencies were calculated for all located stationary structures to verify whether they are minima or transition states. Zero-point energies and thermal corrections were taken from unscaled vibrational frequencies, and the wavefunctions were checked for spin contamination. Free energies of activation, unless otherwise stated, are given for 25 °C. Energy values were refined by single-point UMP2[31] calculations of the UBHandHLYP-optimized gas-phase geometries. Solvent effects, unless otherwise stated, were calculated in dichloromethane by performing single-point PCM[32] calculations on the corresponding gas-phase geometries. All bond lengths are given in Å and the energies in kJ mol^{-1}. Activation energies were calculated relative to the reagents.

Supporting Information (see footnote on the first page of this article): Additional TS structures with the corresponding activation energies, cartesian coordinate matrices and electronic energies for all calculated structures.

Acknowledgments

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